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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/798,486

03/11/2004

Gary L. Cantrell

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12/15/2006

Mallinckrodt Inc.
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EXAMINER

SCHLIENTZ, LEAH H

ART UNIT

PAPER NUMBER

1618

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/798,486

Applicant(s)

CANTRELL, GARY L.

Examiner

Leah Schlientz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 3/11/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/3/04 and 6/9/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not specifically teach the concept that *each* polar head group having a straight-chained hydrophobic group has a different chain length from an adjacent hydrophobic group. For example, Figure 1 shows three adjacent hydrophobic groups which have the same carbon chain length (see middle of figure). This is a new matter rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

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351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Unger *et al.* (US 5,585,112).

Unger discloses a composition for use as an ultrasound contrast agent in methods of imaging comprising microbubbles encapsulating a gas within a shell made of a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon length (i.e. phospholipid blends, charged lipid blends, fatty acids, etc. and *combinations thereof*). See abstract and column 20, lines 31 – 68). The components of the surfactant blends taught by Unger (e.g. fatty acids, phospholipids, etc.) have polar head groups and hydrophobic groups. Lipids bearing hydrophilic polymers such as polyethylene glycol are also disclosed by Unger (column 21, lines 3 – 15). The vessicles may be formed as a monolayer (i.e. wherein the hydrophobic group would be oriented toward the gas in aqueous solution) (column 21, lines 1 – 2).

It is interpreted that when a mixture or blend of fatty acids which may have different carbon chain lengths are employed in the preparation of microbubbles, the microbubble would inherently be organized via self assembly such that a hydrophobic group with a given chain length would be adjacent to another hydrophobic group with a different chain length. This interpretation is supported by applicant's own specification, wherein "without being bound to any theory, it is believed that the enhanced stability of the present invention is due to the longer carbon chains assembling beneath the shorter carbon chains because of the interaction with the gas that is encapsulated."

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Furthermore, it is noted that the recognition of a new property (e.g. enhanced rigidity) over conditions which are otherwise known in the prior art (i.e. the utilization of mixed carbon chain length in microbubble preparation) is not itself patentable. Compositions which are the same have the same properties.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness *et al.* (US 5,536,490).

Klaveness teaches a composition for use as an ultrasound contrast agent in methods of imaging comprising microbubbles encapsulating a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon length (i.e. amphiphilic phospholipids and polymer conjugates), see abstract, columns 2 – 5, lines 1+ and the examples. The amphiphiles contain 10 – 30 carbon atoms (column 4, lines 60 – 6). The vesicles are *capable of* being crosslinked (i.e. crosslinkable), and microbubbles which are not crosslinked are also taught (column 1, lines 60 - 65 and example 4). The components of the shell forming polymer systems comprise polar head groups and hydrophobic groups within their chemical makeup. Klaveness also discloses amphiphiles of formula II in column 5, where R10 is a lipophilic group (e.g. an alkyl) and X is a carboxylate, and PEG derivatives (see column 5 – 7).

It is interpreted that when a mixture or blend of fatty acids which may have different carbon chain lengths are employed in the preparation of microbubbles, the microbubble would inherently be organized via self assembly such that a hydrophobic

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group with a given chain length would be adjacent to another hydrophobic group with a different chain length. This interpretation is supported by applicant's own specification, wherein "without being bound to any theory, it is believed that the enhanced stability of the present invention is due to the longer carbon chains assembling beneath the shorter carbon chains because of the interaction with the gas that is encapsulated."

Furthermore, it is noted that the recognition of a new property (e.g. enhanced rigidity) over conditions which are otherwise known in the prior art (i.e. the utilization of mixed carbon chain length in microbubble preparation) is not itself patentable. Compositions which are the same have the same properties.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Rasor *et al.* (US 5,141,738).

Rasor teaches contrast media for ultrasonic diagnostics comprising microparticles adapted for use when mixed with an injectable aqueous liquid, which comprises an admixture of at least one C₈-C₂₀ fatty acid and at least one non-surfactant physiologically acceptable water soluble solid, and an amount of gas effective to produce a suspension of microbubbles when the microparticles are dispersed in water (column 5, line 61 – column 6, line 11). These contrast media are useful for imaging, after intravenous injection, the heart valves, myocardium etc. (abstract). The fatty acid is myristic, palmitic, stearic, arachic acid or a *mixture thereof* (claim 4), and the physiologically acceptable water-soluble solid component is an inorganic salt, for example (claim 1).

It is interpreted that when a mixture of fatty acids which may have different carbon chain lengths are employed in the preparation of microbubbles, the microbubble would inherently be organized via self assembly such that a hydrophobic group with a given chain length would be adjacent to another hydrophobic group with a different chain length. This interpretation is supported by applicant's own specification, wherein "without being bound to any theory, it is believed that the enhanced stability of the present invention is due to the longer carbon chains assembling beneath the shorter carbon chains because of the interaction with the gas that is encapsulated." Furthermore, it is noted that the recognition of a new property (e.g. enhanced rigidity) over conditions which are otherwise known in the prior art (i.e. the utilization of mixed carbon chain length in microbubble preparation) is not itself patentable. Compositions which are the same have the same properties.

Claims 1 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Church (US 6,045,777).

Church teaches microparticles with enhanced echogenicity for ultrasound imaging (abstract). Incorporation of hydrophobic compounds is effective in stabilizing the echogenicity of polymeric microparticles having gas encapsulated therein, especially fluorinated gases such as perfluorocarbons (column 12, lines 30 – 36). Lipids which may be used to stabilize gas inside the microparticles include fatty acids, phospholipids, etc., including mixtures of fatty acids between 6 and 24 carbon atoms (column 12, lines 36 – 67). It is noted that the microparticles taught by Church may contain additional

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components, but the open-ended comprising language of the instant claims does not exclude the presence of additional components.

It is interpreted that when a mixture of fatty acids are employed which may have different carbon chain lengths, the microbubble would inherently be organized via self assembly such that a hydrophobic group with a given chain length would be adjacent to another hydrophobic group with a different chain length. This interpretation is supported by applicant's own specification, wherein "without being bound to any theory, it is believed that the enhanced stability of the present invention is due to the longer carbon chains assembling beneath the shorter carbon chains because of the interaction with the gas that is encapsulated." Furthermore, it is noted that the recognition of a new property (e.g. enhanced rigidity) over conditions which are otherwise known in the prior art (i.e. the utilization of mixed carbon chain length in microbubble preparation) is not itself patentable. Compositions which are the same have the same properties.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 – 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Unger (US 5,585,112) or Klaveness (US 5,536,490).

Unger and Klaveness disclose a composition for use as an ultrasound contrast agent in methods of imaging comprising microbubbles encapsulating a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon chain length (i.e. phospholipids blends, amphiphilic polymer conjugates, etc.) as set forth above. Unger teaches the use of various shell materials and combinations thereof which are bipolar compounds and are encompassed by the claimed formula, such as fatty acids of up to 22 carbon atoms which are linked to a polymer (e.g. PEG) via an amide group (column 22, lines 20 – 39). Klaveness teaches the use of bipolar compounds having intermolecular regions of mixed carbon length as encompassed by formulas I and II (column 4 – 5).

Unger and Klaveness fail to specifically disclose (i.e. exemplify) blends of shell materials that encompass the compounds having polar head groups and hydrophobic groups encompassed by the formula set forth in the claims.

However, both Unger and Klaveness clearly teach that various combinations of shell forming materials may be used in the microbubbles to form stable microbubbles which are useful for encapsulating a gas and can be administered safely and effectively as an ultrasound contrast agent (e.g. Unger teaches combinations of all taught shell

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materials in columns 20 – 22 and column 29, lines 47+.) Klaveness teaches combinations of shell materials (see column 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use a combination (or blend or mixture) of any encompassed by the claimed formula because both Unger and Klaveness teach that such shell materials in a microbubble for a stable, safe, and effective ultrasound contrast agent to improve methods of ultrasound imaging.

Conclusions

No claims are allowed at this time.

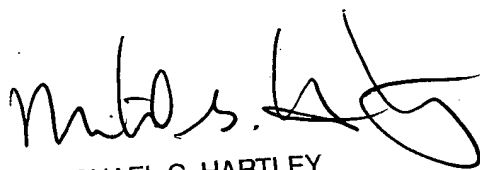
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS



MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER